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Recent Progresses in Idiopathic Generalized Epilepsy Foci Detection Based on Brain Network Analysis

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Abstract

Along with the development of medical assistant techniques, brain network is becoming an important tool for analysing brain nervous system diseases and researching the pathogenesis of diseases. Epilepsy is one of the common brain nervous system diseases, and it has been popular in researches. Idiopathic generalized epilepsy (IGE) is a set of epilepsy syndrome with no other obvious causes besides genetic factors, accounting for about 30% of all kinds of epilepsies. This article summarizes recent progresses in IGE foci detection based on brain network analysis, mainly focusing on the applications in IGE, including functional and structural brain network. Moreover, trends in future development of brain network applications in IGE have been predicted.

Keywords

Idiopathic Generalized Epilepsy; Brain Network; Foci Detection

Introduction

Epilepsy is a chronic nervous system disease caused by excessive synchronous abnormal discharge of neurons (Skjei et al.). Presently, epilepsy can be classified into four categories according to the pathogenesis: idiopathic epilepsy, cryptogenic epilepsy, symptomatic epilepsy and provoked seizures (Shorvon et al.). Idiopathic epilepsy is a set of epileptic disorders with a strong underlying genetic basis, typical manifestations and abnormal electroencephalogram (EEG) test results. Idiopathic generalized epilepsy (IGE), also known as genetic generalized epilepsy (GGE), is one of the most common idiopathic epilepsies, accounting for about 30% of all kinds of epilepsies (Jiang et al., 2013). IGE can be further classified into several subtypes, including childhood absence epilepsy (CAE), juvenile myoclonic epilepsy (JME) and generalized tonic-clonic seizures (GTCS) (Engel et al.).

Nowadays, along with the development of brain network technology, utilizing imaging technology test results to build brain network and analysing its topology based on graph theory has become an established means by which to detect the lesions that cause diseases of the nervous system. Thus, researchers are able to have a deeper, more comprehensive understanding of IGE pathophysiology.

One review (Alexander-Bloch et al.) has shown that brain network construction involves node definition, connectivity construction and graph theory analysis. First, brain parcellation is achieved based on brain atlases or templates (Tzourio-Mazoyer et al.; Desikan et al.; Eickhoff et al.; Lancaster et al.; Craddock et al.) by which each brain region is defined as a single node; then connectivity between nodes can be generated through tracking (Le et al.) or statistical correlating (Liang et al.); finally, properties and features of the network's topological structure can be analysed through graph theory (Watts et al.; Boccaletti et al.).

This article first introduces functional brain network and its application in IGE, next turns to structural brain network and its usage in IGE research; finally, trends in future development of IGE lesions detection based on brain

network analysis are predicted.

Functional Brain Network

Functional brain network is built based on the dependence between the activities or functions of corresponding brain regions through statistical analysis of the time signal sequence between separated brain regions. Therefore, functional brain network is an effective means for describing the model of how spatial separated brain regions work together (Jiang et al., 2009). By studying functional MRI (f-MRI) based brain network, researchers found that some brain regions in IGE patients, such as the prefrontal cortex, appear to reduce functional connectivity (FC); furthermore, most patients with IGE showed a weaker degree of brain network clustering; some brain areas show negative connectivity in seizure duration, such as the medial prefrontal. Compared with the f-MRI brain networks, although the EEG brain network's ability to distinguish brain regions is relatively weak, the time resolution is much higher, and can detect changes in brain network FC at different frequencies. FC of IGE patients is mainly increased at low frequencies and reduced at high frequencies detected based on EEG brain network analysis.

F-MRI Based Brain Network

F-MRI is the abbreviation for blood oxygen level dependent (BOLD) functional-MRI. BOLD is an imaging technique based on the magnetic susceptibility of hemoglobin and deoxyhemoglobin. When nervous tissue function is activated, the local number of hemoglobin and deoxyhemoglobin varies according to changes in local magnetic susceptibility, enabling indirect observation of the condition of local neuronal activity (Kalamangalam et al.; Zhang et al., 2012), therefore, the construction of f-MRI brain function network is mainly based on different brain regions' BOLD signal in time correlation. The most commonly used softwares are SPM (Statistical Parametric Mapping) (http://www.fil.ion.ucl.ac.uk/spm/) and DEPARSF (Data Processing Assistant for Resting-State f-MRI) (http://www.restfmri.net/forum/DPARSF). F-MRI brain functional network has now become one of the most extensively researched means in brain network research and plays an important role in the detection of epileptic foci (Berl et al.;Vlooswijk et al.; Widjaja et al.; Jacobs et al.).

Researches about IGE and its subtypes are mostly based on f-MRI brain network. For instance, McGill et al. found patients with IGE showed markedly reduced FC between anterior and posterior cortical seed regions; seizure duration positively correlates with resting state FC between parahippocampal gyri and the posterior cingulate cortex (PCC) and negatively correlates with FC between the PCC and frontal lobe. Luo et al. used cross-correlation FC analysis with seeding at the posterior cingulate cortex, as well as region-wise calculation in the default mode network (DMN). Results revealed decreased integration within DMN in the absence epilepsy patients; region-wise FC among the frontal, parietal, and temporal lobes was significantly decreased in the patient group and FC between the frontal and parietal lobe showed a significant negative correlation with epilepsy duration. Kim et al., in 2014, used neuropsychological assessment to reveal that patients with IGE had poorer performance than controls on most of the frontal cognitive functions; FC analysis seeding at the anteromedial thalamus revealed a reduction of thalamocortical FC in the bilateral medial prefrontal cortex and precuneus/posterior cingulate cortex in patients with IGE; thalamocortical FC strength of bilateral medial prefrontal cortex correlated negatively with disease duration, but did not correlate with seizure frequency or frontal cognitive functions in patients. As for CAE studies, Masterton et al. found there were marked differences between CAE patients and controls in whole brain FC: patients had decreased FC in the thalamus and basal ganglia and increased FC in the medial occipital cortex. Killory et al. found patients demonstrated significantly impaired FC between the right anterior insula/frontal operculum and medialfrontal cortexrelative to controls. Studies of subtypes GTCS, such as in 2014, Yang et al. found IGE-GTCS patients showed significant increases in voxel-mirrored homotopic connectivity (VMHC) in the bilateral anterior cingulate and medial prefrontal gyrus; no areas showed decreased VMHC in patients; VMHC in the bilateral thalamus, orbital frontal cortex as well as cerebellum showed significant negative correlations with the seizure duration. Wang et al. found decreased functional connectivity in the self-referential, somatosensory, visual, and auditory networks; both decreased and increased FC in the classic default-mode and dorsal attention networks were found in GTCS patients; the present study revealed a negative correlation between the seizure duration and FC changes in the medial prefrontal cortex in GTCS patients.

EEG Based Brain Network

In EEG, electrodes are placed on specific locations on the scalp; EEG technology collects the microvolt signals produced by the brain's neuronal activity (Casson et al.). When building a brain network, EEG needs not define separate brain regions, as the scalp electrons represent brain network nodes; the correlation between the time series of the two electrodes is the connectivity of the brain network. At present, the most commonly used software is NeuroGuide Deluxe (www.appliedneuroscience.com).

Compared with f-MRI brain network research, EEG brain network research is less popular nowadays. In 2011, Clemens et al. found the anatomical patterns of the FC differences showed great frequency-dependency: hemispheric asymmetry was prominent within most very narrow bands of 1Hz bandwidth (VNBs); decreased FC in the IGE group was found across all VNBs in the 1-6 Hz frequency range as compared to mixed patterns comprising both increased and decreased FC at >6 Hz frequencies; in the 5-25 Hz range, decreased FC dominated in the anterior cortex, with increased FC in the posterior parts of the cortex. In 2013, Clemens et al. found maximum abnormalities: increased FC in delta, theta, alpha1 band and decreased FC in alpha2 and beta band in the JME group, mainly among cortical areas that are involved in sensory-motor integration; nodal degree and efficiency of medial, and basal frontal nodes were greater in JME in the alpha1 band; preictal delta FC showed further increase in the above-mentioned areas, as compared to the interictal state.

EEG-fMRI Based Brain Network

F-MRI has a high spatial resolution, but the temporal resolution is limited because image acquisition is time consuming. Therefore, it leads to potential errors in distinguishing the original regions with changing BOLD signals because most early epileptiform neuronal discharges quickly spread to other brain regions. However, EEG signals have millisecond temporal resolution, thus compensating for disadvantages in f-MRI (Zhang and Qian et al., 2011; Li et al.). Furthermore, for purpose of avoiding task stimuli interference, research on neurological system disease is mostly based on a resting brain state. A resting brain state refers to the state of the brain's spontaneous activity (Qiao et al.). However, since it is impossible to guarantee the absence of such behaviours as thinking or inhibited thought in subjects, it is difficult to obtain an accurate brain resting state, causing difficulty in detecting neurological system diseases. Combining EEG and f-MRI technology enables neurologists to simultaneously monitor functional brain activity from two perspectives, thus enabling a more accurate study of the dynamic process of resting state brain systems and the impact of neurological system disease on them (Laufs et al.). EEG-fMRI brain networks use synchronous EEG results to assist f-MRI brain network analysis, and vice versa. In recent years, there are more and more applications for EEG-fMRI brain networks in epileptic lesion detection (Gotman et al.; Vulliemoz et al.; Fahoum et al.; Centeno et al.), such as the finding that seizure discharge may affect brain regions far beyond the assumed lesion area. However, EEG-fMRI technology still has few relevant applications in IGE. In 2013, Yang et al. found decreased functional connectivity within each of these three networks in the CAE patients during interictal generalized spike-wave discharges. It included precuneus-dorsolateral prefrontal cortex (DLPFC), dorsomedial prefrontal cortex (DMPFC) and inferior parietal lobule in the DMN; DLPFC-inferior frontal junction and pre-supplementary motor area (pre-SMA) subregions connectivity disruption in CCN; ACC-ventrolateral prefrontal cortex (VLPFC) and DMPFC in affective network (AN). There were also some regions, primarily the parahippocampus, paracentral in AN, and the left frontal mid orb in the CCN, which showed increased connectivity.

Structural Brain Network

Structural brain networks developed earlier; however, given that the invasive methods of accessing brain structure and connections in animals cannot be used to study the brain in vivo, this hampers research of human brain structural networks. Thanks to researches of Basser et al. on DTI and studies of He et al. on MRI, technologies enabling direct access to information about the living human brain's structure and connection is now possible, leading to development in structural brain networks (Liang et al.; Jiang et al., 2009). Furthermore, studies on structural brain networks constructed from DTI found weakened small-worldness, as well as damage to the sub-network and negative connections in seizure duration of IGE patients. At present, there are still relatively few studies on structural brain networks constructed from MRI; existing research has found that in certain areas of the brains of IGE patients, brain connectivity varies significantly.

DTI Based Brain Network

DTI is the only technique that uses non-invasive diagnosis to track the directional movement of water molecules through white matter, allowing understanding of physiological tissue and pathological states on a microscopic scale (Bai et al.). The most commonly used softwares include PANDA (Pipeline for Analyzing Brain Diffusion Images) (http://www.nitrc.org/projects /panda/) and DTI-TK (Diffusion Tensor Imaging Toolkit) (http://dti-tk.sourceforge.net/pmwiki/pmwiki. php). DTI is also one of the hot areas in brain network research, particularly useful in exploring aspects of brain structures (Gong et al.; Cheng et al.; Han et al.), though providing few applications in IGE.

Zhang et al. found significant decreases in the clustering coefficient, indicating a shift to random brain network in IGE-GTCS patients in 2011. Caeyenberghs et al. found JME patients exhibited a small world topology in their white matternetworks, with no significant differences in the global multivariate network properties between the groups; the network-based statistic approach identified one subnetwork of hyperconnectivity (https://www.wordnik.com/words/hyperconnect ivity) in the JME group, involving primary motor, parietal and subcortical regions; there was a significant positive correlation in structural connectivity with cognitive task performance. Xue et al. also found CAE patients showed small-world properties in their white matter (WM) networks; the network connection strength, absolute clustering coefficient, and global/local efficiency decreased significantly, while the characteristic path length increased significantly in CAE patients compared with the controls; significantly decreased WM connections, nodal properties, and impaired sub-networks were found in the sub-cortical structures, orbitofrontal area, and limbic cortexes of CAE patients; network connection strength, local efficiency, and nodal features in some regions were significantly negatively correlated with the duration of epilepsy.

MRI Based Brain Network

MRI can generate high-resolution grayscale images (Barsi et al.), which contain plenty of morphological information, including cortical thickness, volume, curvature, complexity and other features. Owing to the limitations of MRI images, at present the majority of MRI brain networks are based on construction between groups (Alexander-Bloch et al.). In 2012, Tijms et al. proposed the individual MRI brain network construction method, and in the following year, Batalleet al. used Tijms et al.'s study as a basis for research on intergroup analysis, thus providing a new perspective on studying structural brain networks constructed from MRI. Commonly used analysis softwares include Freesurfer (http://freesurfer.net/), VBM (Voxel-Based Morphometry) (http://dbm.neuro.uni-jena.de/vbm/), ANIMAL (Automatic Non-linear Image Matching and Anatomical Labeling) (https://www.mcgill.ca/bic/softwarealass/servicessoftwareadvancedimageprocessingtoolsbeast/anatomical-imaging/animal), and so on.

Currently, there is insufficient research analysing IGE based on structural brain networks constructed from MRI, with studies still primarily focused on morphology (Betting et al.; Kim et al., 2007; Ronan et al.; Saini et al.; Kim et al., 2013; Huang et al.). For example, Betting et al. found increased gray matter density in the frontal end of JME patients' brains, an increase in volume of gray matter in the bilateral prefrontal area, coupled with a reduction in the volume of bilateral thalamic gray matter; Kim et al. found volume reduction in the ventral and dorsal sides of the bilateral thalamus in patients with IGE in 2013; Huang et al. found that patients with GTCS in the bilateral thalamus, prefrontal, insular cortex and cerebellum showed gray matter volume reduction, with gray matter volume in the bilateral thalamus and the left medial frontal gyrus negatively correlated with seizure duration. Within the body of literature on structural brain networks constructed from MRI, only study of Bernhardt et al. has found those IGE patients' structural connections increase in the frontal and parietal regions, but decrease in the marginal region.

Conclusions

Although researchers have done extensive studies on various brain networks and their applications in IGE, because the field of brain network research only recently emerged, there is still a big gap compared with other mature methods, such as BOLD image, EEG signals, fractional anisotropy of white matter fibre tracts and structural morphological features analysis. Here, a review has been made of consulted literatures.

First, the uneven development of various types of brain network is notable, especially when it comes to IGE study.

There are abundant researches and research teams based on f-MRI brain networks. In contrast, similar research on functional brain network, namely EEG brain research, is less popular, with main research results chiefly produced by the Clemens team. Compared with functional brain network, research about structural brain network is far from ideal, and existing MRI-based studies are considerably fewer than DTI-based studies.

Second, there are few quantitative analyses. In IGE studies, regardless of structural or functional brain network, changes in brain connectivity are found in certain brain regions of patients. But there is no definite conclusion about the extent of such change; most studies give only qualitative conclusions.

Third, there are few studies on the combination of structural and functional brain networks. Most studies of brain networks in IGE are still using one of the single methods, but combining structural and functional networks for analysis can unearth more information to explain the etiology and pathology of IGE.

In summary, future research should be based on a variety of joint detection methods. For one thing, this can improve the accuracy of test results; for another, it can uncover more information. Future studies must also investigate methods for evaluating the validity and accuracy of research results, especially when it comes to defining the standard for comparing multiple models. Furthermore, the clinical application of research methods should also be strengthened. Currently, IGE researches are mostly based on comparison between two groups, which is usually done through registration of subjects' brain images during preprocessing in order to reduce individual differences, but clinical diagnosis is for a single patient, in which case the individual differences are particularly important. With the emergence of the individual MRI brain network construction method, all kinds of future brain networks are expected to realize the direct construction of individual brain networks. MRI and EEG are the most common clinical diagnostic tools, so future studies should focus on brain networks constructed from EEGs and MRIs, as well as their applications in IGE.

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